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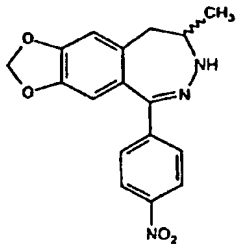
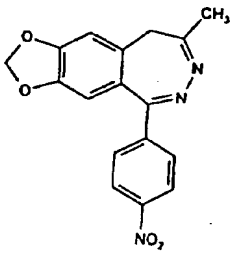
(57) Abstract

The invention relates to the (+)- and (-)-enantiomers of the compounds of formula (I) as well as a process for the preparation of these enantiomers. This process comprises reducing 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine of formula (II) by using an adduct formed from an (R)- or (S)-, respectively, 2-amino-1,1-diphenyl-alkan-1-ol derivative of general formula (III), wherein R_1 and R_2, which are different, stand for a straight or branched chain C_{1-4} alkyl group or an unsubstituted phenyl or benzyl group, with one molar equivalent of borane or a borane complex. The enantiomers of the compound of formula (I) are valuable intermediates in the synthesis of therapeutically active compounds.



(I)



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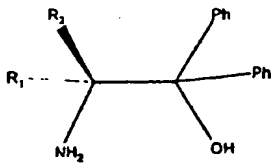

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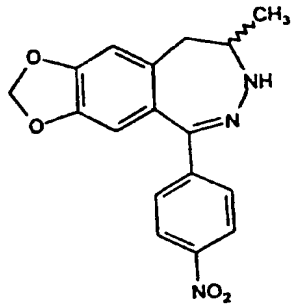
OPTICALLY ACTIVE 1-(4-NITROPHENYL)-4-METHYL-7,8--METHYLENEDIOXY-3,4-DIHYDRO-5H-2,3-BENZODIAZEPINE AND PROCESS FOR PREPARING SAME

This invention relates to the enantiomers of 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H--2,3-benzodiazepine of the formula (I)



(I)

and a process for the preparation of these enantiomers, which are valuable intermediates in the synthesis of therapeutically useful substances.

It is known from the Hungarian patent specifications Nos. 198,494 and 206,719 as well as from the published European patent application No. 492,485 and from publications [Bioorg. Med. Chem. Lett. 3, 99 (1993); Eur. J. Pharm. 224, 293 (1993)] that 1-(4-aminophenyl)-3--acyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepines, e.g. the 1-(4-aminophenyl)-3-acetyl-4--methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine and 1-(4-aminophenyl)-3-(N-methylcarbamoyl)-4--methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine, possess anticonvulsive, muscle relaxant and neuroprotective effects. The basis of these valuable pharmacological effects is a noncompetitive antagonism of quisqualate/AMPA receptors. Furthermore, 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepine and 1-(4-acetylaminophenyl)-4-methyl-7,8-

-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine are dopamine-uptake-inhibiting and psychostimulatory in their character; therefore, these compounds may potentially be useful for the treatment of parkinsonism.

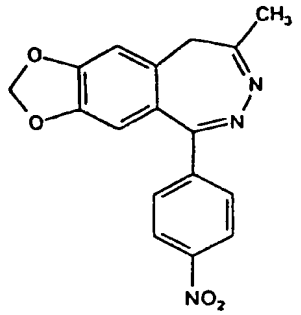
These compounds have chiral structure. As a result of their synthesis described earlier they are formed as racemates from a common intermediate, namely, from the racemic 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy--3,4-dihydro-5H-2,3-benzodiazepine of formula (I).

It is known that the pure enantiomers of biologically active compounds may be very different from the viewpoint of both their main biological effects as well as toxicity, pharmacokinetics and metabolism. Thus, in the development of novel drugs it is aimed to prepare optically pure enantiomers and some official prescriptions are directed to the same purpose [see e.g.: Development of Chiral Drugs in an Evolving Regulatory Environment. Regulatory Affairs 3, 483 (1991)].

Although the racemic active compounds listed above and their precursors having a racemic structure can in principle be resolved by using traditional methods, the most preferred possibility of preparing optically pure enantiomers consists in that the enantiomers of the first chiral molecule of the synthesis, in the given case the compound of formula (I), are prepared and the subsequent steps of the synthesis are carried out by starting from these enantiomers. Whereas the traditional resolution based on the separation of diastereomeric salt or compound pairs can theoretically provide the pure enantiomers of a racemic compound in a yield of at most 50%, by using an enantioselective chemical reaction in the step resulting in the development of chirality, the desired enantiomer(s) can be prepared in yields substantially higher than 50 %.

Thus, the invention is aimed at providing a

process, by which the double bond in 3,4-position of the achiral derivative of formula (II)



(II)

can enantioselectively be reduced to obtain in this way the enantiomers of the compound of formula (I) in a high yield and high optical purity.

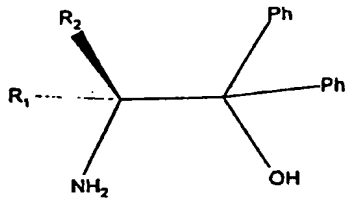
Some methods are known in the literature for the enantioselective reduction of imino compounds. According to one of these methods the reduction is carried out by using diphenylsilane or hydrogen in the presence of complexes or transition metal salts formed with optically active tertiary phosphine ligands as homogeneous catalysts [Tetrahedron Letters **49**, 4865 (1973); Angew. Chem. Int. Ed. Engl. **24**, 995 (1985); J. Chem. Soc. Chem. Comm. **6** (1975); Tetrahedron: Asymmetry **4**, 215 (1993)].

Other authors use a chiral triacyloxy borohydride as reducing agent for enantioselective reductions, where the chiral reducing reagent is most frequently prepared from N-acylproline and sodium borohydride *in situ* [Tetrahedron Letters **22**, 3869 (1981); J. Chem. Soc. Perkin Trans. I, 265 (1983); Chem. Pharm. Bull. **31(1)**, 70 (1983); Heterocycles **29**, 1283 (1989); J. Het. Chem. **28**, 329 (1991)]. According to an other method reductive complexes formed from optically active 1,2-aminoalcohols and 2 molar equivalents of borane are useful for enantioselective reductions [J. Chem Soc. Perkin Trans. I, 2039 (1985); *ibidem* 3200 (1990); Tetrahedron: Asymmetry **3**, 337

(1992)].

Each of the above methods have been used for specific individual groups of imino compounds; moreover, within these groups the enantiomeric purity of the primary products was strongly dependent on the substituents of the given imino compound.

Surprisingly, it has been found that 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine of formula (II) can enantioselectively be reduced by using in a small excess an adduct formed from a 2-amino--1,1-diphenylalkan-1-ol of the general formula (III),



(III)

having R or S configuration, respectively, with 1 molar equivalent of borane or a borane complex and in this way, 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine of formula (I) can simply be prepared in a good yield with a high enantiomeric purity.

According to the invention, the peparation of enantiomers of 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy--3,4-dihydro-5H-2,3-benzodiazepine of formula (I) comprises reducing 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine of formula (II) by using an adduct formed from an (R)- or (S)-, respectively, 2--amino-1,1-diphenylalkan-1-ol derivative of formula (III), wherein

R_1 and R_2, which are different, stand for hydrogen; a straight or branched chain C_{1-4} alkyl group; or an unsubstituted phenyl or benzyl group,

with one molar equivalent of borane or a borane complex.

As mentioned above, the enantiomers of the compound of formula (I) are valuable intermediates which, after acylation and subsequent reduction, lead to the enantiomers of 1-(4-aminophenyl)-3-acyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepines, which are antagonists of the quisqualate/AMPA receptors; or, by reducing and then, if desired, acetylating the enantiomers of the compound of formula (I), 1-(4-aminophenyl)-4-methyl--7,8-methylenedioxy-3,4-dhydro-5H-2,3-benzodiazepine and 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4--dihydro-5H-2,3-benzodiazepine can be obtained, which have psychostimulant character.

According to a preferred embodiment of the process of the invention the (R)- or (S)-1,2-aminoalcohol, respectively, of general formula (III), wherein R_1 and R_2 are as defined above, is dissolved in anhydrous methylene chloride or in a higher aliphatic halohydrocarbon and reacted with 1 molar equivalent of borane at a temperature between 0 °C and -70 °C, then left to stand at a temperature between 0 °C and 10 °C for 15 to 20 hours and finally the reductive complex obtained is reacted with the compound of formula (II) preferably dissolved in the same anhydrous solvent at a temperature between 0 °C and the boiling point of the solvent, preferably between 25 °C and 60 °C. The reaction mixture is suitably worked up as follows: the mixture is mixed with sodium carbonate solution, the organic phase is washed with water until neutral and evaporated under reduced pressure. The crystalline product obtained is suspended in a C_{1-3} alkanol, preferably ethanol, and the product is isolated by filtration.

The primary product obtained is characterized by its specific rotary power. The enantiomeric purity of the product is qualified by the percentage of enantiomers, which can be determined by the following methods:

1) by ^{1}H-NMR techniques using a complex of paramagnetic rare earth element (shift reagent); or
2) by high pressure liquid chromatography (HPLC) on a column containing a chiral sorbent.

According to our investigations, the primary product has a high enantiomeric purity, which can be increased nearly to 100% even by a single recrystallization.

The preparation of 5H-2,3-benzodiazepine derivative of formula (II) used as starting substance in the process according to the invention is described in the Hungarian patent specification No. 191,702. The 1,2-aminoalcohols of general formula (III) are known compounds, which can be synthetized on the basis of literature references [J. Org. Chem. 49, 555 (1984); J. Chem. Soc. Perkin Trans. I, 2039 (1985); and Japanese patent specification No. 81-65,847 (Chem. Abstr. 95, 203530g)].

The invention is illustrated in detail by the following non-limiting Examples.

Example 1

(-)-1-(4-Nitrophenyl)-4-methyl-7,8-methylenedioxy--3,4-dihydro-5H-2,3-benzodiazepine

Method A

To a solution conaining 4.75 g (18.6 mmol) of (S)--(-)-2-amino-1,1-diphenyl-3-methylbutan-1-ol in 50 ml of anhydrous methylene chloride, 9.5 ml (17 mmol) of an 1.8 M tetrahydrofuran solution of borane-tetrahydrofuran complex were dropwise added at -70 °C under dry nitrogen in 20 minutes. The temperature of the solution was gradually increased to 0 °C during 3 hours and then maintained at 4 °C for 15 hours.

A solution containing 5.0 g (15.5 mmol) of 1-(4--nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 100 ml of dry methylene chloride was dropwise added to the above solution at room temperature

during one hour while stirring. After allowing the reaction mixture obtained to stand at room temperature for 10 days, 10% aqueous sodium carbonate solution was added and the mixture was stirred for 30 minutes. The organic phase was separated, washed twice with 50 ml of water each, dried over anhydrous sodium sulfate and evaporated under reduced pressure. After suspending the crystalline residue in 50 ml of ethanol, the orange-yellow crystals were filtered, washed twice with 5 ml of ethanol each and dried at 50 to 60 °C to obtain 4.47 g (88.6%) of product, $[\alpha]_D^{25}$ = -118° (c = 1, chloroform).

The ratio of (-) enantiomer to the (+) enantiomer was found to be 90:10 as determined by ^{1}H-NMR spectroscopy by using Eu(hfc)$_3$ shift reagent (by weighing 5 mg of shift reagent to 10 mg of substance and dissolving this mixture in deuterochloroform).

After dissolving in 54 ml of hot ethyl acetate, the primary product was allowed to crystallize at room temperature for 15 hours. The crystalline precipitate was filtered, washed 3 times with 5 ml of ethyl acetate each and dried at 50 to 60 °C to obtain 2.87 g (56.9%) of the aimed compound, $[\alpha]_D^{25}$ = -155.6° (c = 1, chloroform), m.p.: 171-172.5 °C. On investigating the ratio of enantiomers, the amount of the minor enantiomer was found to be lower than 1 % as determined by using either ^{1}H-NMR spectroscopy or simultaneously HPLC analysis [CHIRALCEL OJ. (Daicel Chemical Industries, LTD)] with a 35:65 mixture of hexane and isopropanol as eluent.

Method B

The method A of Example 1 was followed, with the difference that the reaction mixture was boiled under reflux for 3 days to give 4.27 g (84.7 %) of product, $[\alpha]^D_{25}$ = -106.1° (c = 1, chloroform) containing the (-) enantiomer related to the (+) enantiomer in a ratio of 87:13 (based on HPLC analysis).

After recrystallizing the primary product from 52 ml of ethyl acetate, 2.80 g (55.6 %) of the aimed product were obtained, $[\alpha]^{D}_{25}$ = -153.6° (c = 1, chloroform), m.p.: 170-172 °C. This product contained the minor enantiomer in an amount lower than 1 % (based on HPLC analysis.

Method C

To a solution containing 4.75 g (18.6 mmol) of (S)--(-)-2-amino-1,1-diphenyl-3-methylbutan-1-ol in 50 ml of dry dichloroethane, 9.5 ml (17 mmol) of an 1.8 M tetrahydrofuran solution of the borane-tetraydrofuran complex were dropwise added at -10 °C under dry nitrogen during 20 minutes. The solution was maintained at +4 °C for 15 hours, then 5.0 g (15.5 mmol) of 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine dissolved in 200 ml of dry dichloroethane were dropwise added during 1 hour while stirring. The reaction mixture obtained was stirred at 60 °C for 30 hours. Thereafter, method A of Example 1 was followed to obtain 4.2 g (83.3 %) of primary product, $[\alpha]_{D}^{25}$ = -106.6° (c = 1, chloroform).

In this product the ratio of the (-) enantiomer to the (+) enantiomer was found to be 87:13 (based on HPLC analysis).

By recrystallizing as described under method A of Example 1, the primary product could be converted to the aimed product having the enantiomeric purity given there.

Method D

By using 10.0 g (37.2 mmol) of (S)-(-)-2-amino-1,1--diphenyl-4-methyl-pentan-1-ol and 19 ml (34 mmol) of an 1.8 M tetrahydrofuran solution of borane-tetrahydrofuran complex as starting substances and following the process described under method A of Example 1, 4.2 g (83.3 %) of primary product were obtained, $[\alpha]_{D}^{25}$ = -142.1° (c = 1, chloroform), which contained the (-) enantiomer related to the (+) enantiomer in a 93:7 ratio (based on HPLC analysis).

Method E

Method A of Example 1 was followed, except that 1.6 ml (17 mmol) of borane-dimethyl sulfide complex were used and the reaction mixture was allowed to stand at room temperature for 4 days to obtain 4.0 g (79.3 %) of primary product, $[\alpha]_D^{25}$ = -106.3° (c = 1, chloroform), which contained the (-) enantiomer related to the (+) enantiomer in an 87:13 ratio (based on HPLC analysis).

Example 2

Method A

(+)-1-(4-Nitrophenyl)-4-methyl-7,8-methylenedioxy--3,4-dihydro-5H-2,3-benzodiazepine

By using 4.75 g (18.6 mmol) of (R)-(+)-2-amino-1,1--diphenyl-3-methyl-butan-1-ol as starting substance and then following method A of Example 1, 4.61 g (91.4 %) of primary product were obtained, $[\alpha]_D^{25}$ = +112° (c = 1, chloroform), which contained the (+) enantiomer related to the (-) enantiomer in an about 9:1 ratio (based on HPLC analysis).

After recrystallizing the primary product as described in Example 1, 3.1 g (61.3 %) of the aimed compound were obtained, $[\alpha]_D^{25}$ = +153.4° (c = 1, chloroform), m.p.: 172-174 °C. This product contained the minor enantiomer in an amount lower than 1% (based on ^{1}H-NMR shift reagent as well as HPLC analysis).

Method B

Method C of Example 1 was followed by starting from 5.0 g (18.6 mmol) of (R)-(+)-2-amino-1,1-diphenyl-4-methylpentan-1-ol and using 1.6 ml (17 mmol) of borane--dimethyl sulfide complex, except that the reaction mixture was stirred at 60 °C for 3 hours to give 4.17 g (82.7 %) of primary product, $[\alpha]_D^{25}$ = +140.6° (c = 1, chloroform), which contained the (+) enantiomer related to the (-) enantiomer in a 93:7 ratio (based on HPLC analysis).

By recrystallizing the primary product from 78 ml of hot ethyl acetate, 3.05 g (60.5 %) of the title compound were obtained, $[\alpha]_D^{25}$ = +155.2° (c = 1, chloroform), m.p.: 172-174 °C, which contained the minor enantiomer in an amount lower than 1% (based on ^{1}H-NMR shift reagent as well as HPLC analysis).

The therapeutically valuable products may be prepared from the enantiomers of formula (I) according to the invention e.g. in the following way.

1. Preparation of (+)-1-(4-aminophenyl)-3-acetyl--4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepine

Step a)

(-)-1-(4-Nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

A suspendion containing 2.34 g (7.2 mmol) of (-)-1--(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro--5H-2,3-benzodiazepine in 11.7 ml of acetic acid anhydride was stirred at room temperature for 2 hours. Subsequently, the reaction solution was mixed with 60 ml of water under cooling with ice, the precipitate was filtered, washed 3 times with water and dried at 80 °C to obtain 2.5 g (94.6 %) of the aimed product, $[\alpha]_D^{25}$ = - 54.9° (c = 1, chloroform), m.p.: 172-177 °C.

Step b)

(+)-1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a suspension containing 2.6 g (7.08 mmol) of (-)-1-(4-nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 52 ml of methanol, 0.5 g of wet Raney nickel catalyst and 1.2 ml (24.8 mmol) of 100% hydrazine hydrate were added and the reaction mixture was stirred for 1 hour. During this time a solution was formed and the inner temperature increased to 40-45 °C.

After filtration the catalyst was washed 3 times with 10 ml of methanol each, the filtrate was evaporated under reduced pressure and the residue was thoroughly triturated with 50 ml of water. The solidified crude product was filtered, washed 3 times with 10 ml of water each and dried to give 2.17 g (90.8 %) of a product which was recrystallized from 14 ml of 50% aqueous ethanol to give 1.92 g (80.4 %) of the aimed product, $[\alpha]_D^{25}$ = +344.5° (c = 1, methanol), m.p.: 168-170 °C.

This product contained the minor enantiomer in an amount lower than 1% [based on ^{1}H-NMR shift reagent method: 4.8 mg of the compound + 8.2 mg of Eu(hfc)$_3$ shift reagent in deuterochloroform; or based on HPLC analysis (CHIRALCEL OF) by using an 1:1 mixture of hexane and isopropanol containing 0.1 % by vol. of diethylamine as eluent].

2. Preparation of (-)-1-(4-aminophenyl)-3-acetyl-4--4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepine

Step a)

(+)-1-(4-Nitrophenyl)-3-acetyl-4-methyl-7,8--methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

The title product was prepared by using (+)-(4--nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H--2,3-benzodiazepine as starting substance and following the method described in step 1.a) to give a yield of 92.7 %, $[\alpha]_D^{25}$ = +49.6° (c = 1, chloroform), m.p.: 173-177 °C.

Step b)

(-)-1-(4-Aminophenyl)-3-acetyl)-4-methyl-7,8--methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By using (+)-1-(4-nitrophenyl)-3-acetyl-4-methyl--7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine as starting substance and following step 1.b), the crude product was obtained in a yield of 91.3 %. This was recrystallized from 50 % aqueous ethanol to give a yield

of 77.5%, $[\alpha]_D^{25}$ = -325.8° (c = 1, methanol), m.p.: 167-170 °C. This product contained the minor enantiomer in an amount lower than 1% (based on ^{1}H-NMR or HPLC analysis).

3. Preparation of (+)-1-(4-Aminophenyl)-3-(N-methylcarbamoyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benezodiazepine

Step a)

(-)-1-(4-Nitrophenyl)-3-(N-methylcarbamoyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

A mixture containing 4.0 g (12.3 mmol) of (-)-1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine, 2.18 ml (37 mmol) of methyl isocyanate and 80 ml of dry methylene chloride was stirred at room temperature for 3 days. Then the solution was evaporated under reduced pressure and the residue was solidified by thoroughly triturating with 60 ml of water.

After filtration the product was washed and dried to obtain 4.49 g (95.5 %) of the aimed product, $[\alpha]_D^{25}$ = = -315.3° (c = 1, chloroform).

Step b)

(+)-1-(4-Aminophenyl)-3-(N-methylcarbamoyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

The title product was prepared by using (-)-1-(4-nitrophenyl)-3-(N-methylcarbamoyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine as starting substance and following the process described in step 1.b) to obtain a product with a yield of 95.14%, $[\alpha]_D^{25}$ = +363.4° (c = 1, chloroform).

This product contained the minor enantiomer in an amount lower than 1% (based on HPLC analysis and ^{1}H-NMR shift reagent method).

4. Preparation of (-)-1-(4-aminophenyl)-3-(N-methylcarbamoyl)-4-methyl-7,8-methylenedioxy-3,4-

-dihydro-5H-2,3-benzodiazepine

Step a)

(+)-1-(4-Nitrophenyl)-3-(N-methylcarbamoyl)-4--methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepine

The aimed product was obtained in a yield of 95.0% by using (+)-1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine as starting substance and following the method described in step 3.a), $[\alpha]_D^{25}$ = +304.1° (c = 1, chloroform).

Step b)

(-)-1-(4-Aminophenyl)-3-(N-methylcarbamoyl)-4--methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3--benzodiazepine

The aimed product was prepared by using (+)-1--(4-nitrophenyl)-3-(N-methylcarbamoyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine as starting substance and following the method described in step 1.b) to give a yield of 95.5%, $[\alpha]_D^{25}$ = -365.9° (c = 1, chloroform).

This product contained the minor enantiomer in an amount lower than 1% (HPLC: CHIRALCEL OF by using a 1:1 mixture of n-hexane and isopropanol containing 0.1% by vol. of diethylamine as eluent; ^{1}H-NMR: 10 ml of product + + 10 or 20 mg of $Eu(hfc)_3$ shift reagent in deuterochloroform).

5. Preparation of (-)-1-(4-aminophenyl)-4-methyl--7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

The aimed product was prepared by using (-)-1-(4--nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H--2,3-benzodiazepine as starting substance and following the process described in step 1.b) to obtain a crude product in a yield of 82.0%, which was recrystallized from 50% aqueous ethanol to give the aimed product,

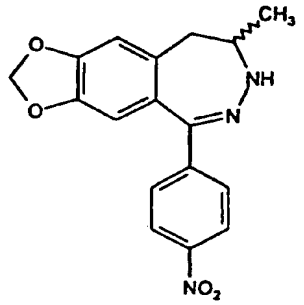
$[\alpha]_D^{25}$ = -250.6° (c = 1, methanol), m.p.: 98-100 °C. This product contained the minor enantiomer in an amount lower than 1% (based on HPLC analysis).

6. Preparation of (+)-1-(4-aminophenyl)-4-methyl--7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

The aimed product was obtained in a yield of 80.9% by using (+)-1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine as starting substance and following the process described in step 1.b). It was purified by recrystallization from 50% aqueous ethanol to give a pure product, $[\alpha]_D^{25}$ = +246.0° (c = 1, methanol), m.p.: 92-94 °C. This product contained the minor enantiomer in an amount lower than 1% (based on HPLC analysis).

Claims

1. Enantiomers of 1-(4-nitrophenyl)-4-methyl-7,8--methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine of formula (I)

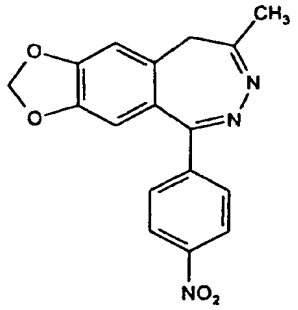


(I)

2. (-)-1-(4-Nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine.

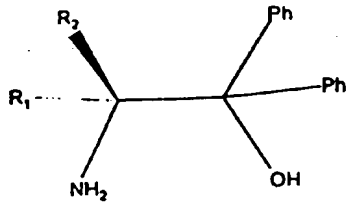
3. (+)-1-(4-Nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine.

4. A process for the preparation of enantiomers of 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4--dihydro-5H-2,3-benzodiazepine of formula (I), which c o m p r i s e s reducing 1-(4-nitrophenyl)-4-methyl--7,8-methylenedioxy-5H-2,3-benzodiazepine of formula (II)



(II)

by using an adduct formed from an (R)- or (S)-, respectively, 2-amino-1,1-diphenyl-alkan-1-ol derivative of the general formula (III),



(III)

wherein R_1 and R_2, which are different, stand for a straight or branched chain C_{1-4} alkyl group or an unsubstituted phenyl or benzyl group, with one molar equivalent of borane or a borane complex.

5. A process as claimed in claim 4, which comprises using (R)- or (S)-, respectively, 2-amino-1,1-diphenyl-3-methylbutan-1-ol as 2-amino-1,1-diphenylalkan-1-ol of general formula (III).

6. A process as claimed in claim 4, which comprises using (R)- or (S)-, respectively, 2-amino-1,1-diphenyl-4-methylpentan-1-ol as 2-amino-1,1-diphenylalkan-1-ol of general formula (III).

7. A process as claimed in any of claims 4 to 6, which comprises using a C_{1-4} aliphatic halohydrocarbon, preferably methylene chloride or 1,2-dichloroethane, as solvent.

8. A process as claimed in any of claims 4 to 7, which comprises carrying out the reaction at a temperature between 10 °C and 100 °C, preferably between 25 °C and 60 °C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 94/00024

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 491/056; A 61 K 31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 491/056

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO, A, 92/11 262 (GYOGYSZERKUTATO INTEZET) 09 July 1992 (09.07.92), claims 1-11.	1-8
A	EP, A, 0 492 485 (GYOGYSZERKUTATO INTEZET) 01 July 1992 (01.07.92), claims 1-7. (cited in the application)	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 1994 (28.11.94)	06 December 1994 (06.12.94)

Name and mailing address of the ISA/ AT	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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